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The Pharmacokinetics of Vincristine in Man:

Reduced Drug Clearance Associated with Raised Serum Alkaline Phosphatase and Dose-Limited Elimination

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Summary. *A radioimmunoassay has been used to investigate the pharmacokinetics of vincristine in 39 cancer patients who received between 0.4 and 1.54 mg vincristine/m² as part of standard treatment protocols. There was wide interindividual variation in both the terminal elimination half-life of vincristine ($t_{1/2}\beta$) and the associated volume of distribution (Vd), resulting in an 11-fold range of dose-corrected area under the plasma concentration versus time curve values ($AUC_{0-\infty}$). Elevated vincristine $AUC_{0-\infty}$ values were observed in those patients with raised serum alkaline phosphatase at the time of vincristine estimation. The $t_{1/2}\beta$ was significantly longer in these patients than in those with serum alkaline phosphatase within normal limits, suggesting that biochemical evidence of cholestasis is associated with reduced clearance of vincristine. Evidence is also presented to suggest that the clearance of vincristine is dose-dependent within the therapeutic dose range. We observed a disproportionate rise in vincristine plasma concentration at doses exceeding 1 mg/m², due primarily to a lengthening of mean $t_{1/2}\beta$ compared with that observed for patients receiving 1 mg vincristine/m² or less.*

Introduction

The antimitotic vinca alkaloid vincristine is widely used in cancer chemotherapy, but peripheral neuropathy presents a serious side-effect, which frequently requires dosage reduction or cessation of therapy [1]. Neurotoxicity is often dose-related, although toxicity unrelated to dose has been reported [7], and there is also evidence that the development of peripheral neuropathy may be influenced by disease state [11]. More recently, comparative pharmacokinetic studies of vincristine, vinblastine, and vindesine have shown a positive correlation between length of drug elimination half-life and neurotoxic potential [6], suggesting that the greater neurotoxicity of vincristine is due to its more prolonged contact with nerve tissue. We have carried out a study of the pharmacokinetics of vincristine in patients who received between 0.4 and 1.54 mg vincristine/m² as part of their treatment protocol, to identify factors that may affect the clearance of this drug and hence influence the incidence and severity of neuropathic side-effects. Since vincristine is primarily excreted by the biliary route [5] we have investigated the relationship between vincristine plasma levels and liver function as indicated by routine biochemical tests. Recent studies indicating that the vinca alkaloids inhibit bile flow [4] suggested to us that the marked increased incidence of neuropathy with increasing dose may reflect saturable elimination of vincristine within the therapeutic dose range. Our results show that elevated plasma levels of vincristine are associated with raised serum alkaline phosphatase and that there is a disproportionate rise in drug exposure at doses above 1 mg/m².

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Patients and Methods

Patients. A total of 39 patients were included in the study, details of whom are shown in Table 1. The majority of patients received vincristine in combination with other drugs. After informed consent had been obtained blood samples were taken prior to drug administration and at regular intervals after therapy. Samples were drawn through an indwelling heparinised catheter fitted with a three-way tap and collected in lithium heparin tubes. Plasma was separated by centrifugation and stored at −20° C until analysis.

Assessment of Liver Function. Liver function was assessed in all patients prior to vincristine injection by measuring serum bilirubin, alkaline phosphatase, lactic dehydrogenase, and transaminases. In

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Table 1. Patient details[a]

	N.H.L.	H.D.	A.L.	M.M.	I.T.P.	B.C.
Number	8	7	15	2	2	5
Male	6	6	8	1	–	–
Female	2	1	7	1	2	5
Mean age	56	48	22	57	31	52
Range	27–70	20–63	4–68	57	16–47	49–65

[a] N.H.L., non-Hodgkin's lymphoma; H.D., Hodgkin's disease; A.L., acute leukaemia; M.M., multiple myeloma; I.T.P., idiopathic thrombocytopenia; B.C., breast carcinoma

the majority of patients serum γ-glutamyl transferase activity was also assessed.

Vincristine Radioimmunoassay. Vincristine plasma concentrations were estimated according to a modification of the radioimmunoassay described by Teale et al. [10]. ^{3}H-Vinblastine (6.3–11.2 Ci/mmole, Radiochemical Centre, Amersham, Bucks, England) was used as tracer and the antisera used at an initial dilution of 1 : 100, when 50% of the added tracer was bound by the antisera in the absence of unlabelled alkaloid. Both vinblastine- and vincristine displaced antisera bound ^{3}H-vinblastine. Non-specific binding of tracer to normal plasma was less than 6%. Clinical-grade vincristine (Eli Lilly & Co., Hampshire, Great Britain) was used to prepare appropriate standards. The limit of sensitivity of the assay was 500 pg vincristine per ml plasma and intra- and interassay variation was less than 4% and 9%, respectively. Other drugs used clinically in combination with vincristine failed to inhibit ^{3}H-vinblastine binding to antisera at therapeutically relevant concentrations. The following pharmacokinetic parameters were determined: half-life of the terminal elimination phase ($t_{1/2}\beta$) and associated volume of distribution (Vd). These parameters were calculated for each patient studied and a programmable calculator was used to determine the line of best fit of the data points by the method of least squares regression analysis. This programme also yielded the area under the vincristine plasma concentration-time curve delineated by the final elimination phase ($AUC_{0-\infty}$) by the trapezoidal rule.

Results

Vincristine plasma concentrations were monitored in 39 patients receiving the drug and several subjects were investigated on more than one occasion. Following IV injection the concentration of vincristine in plasma fell bi-exponentially over the period of study (Fig. 1), and data points could be fitted to a two-compartment pharmacokinetic model according to the following formula:

$$c_p = A_{\exp}{}^{-\alpha t} + B_{\exp}{}^{-\beta t}. \quad [3]$$

In agreement with earlier studies [4], we observed that the initial fall in vincristine plasma concentration, representing distribution, was rapid (mean $t_{1/2}\alpha$ = 8.2 min) compared with the subsequent elimination

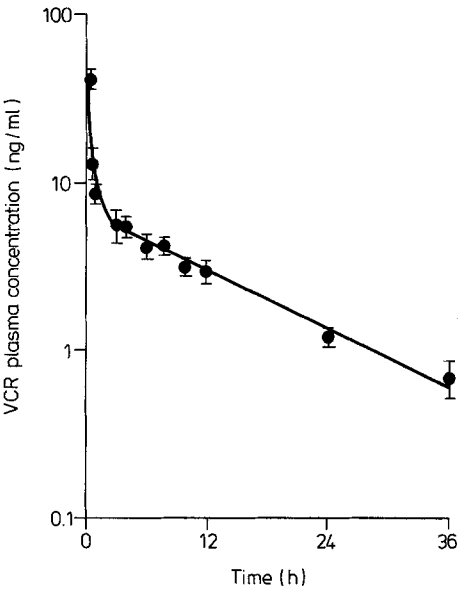

Fig. 1. Plasma concentration of vincristine following IV bolus injection. Patient S. B., dose 1 mg/m^2

Table 2. Mean values of vincristine pharmacokinetic parameters in 39 subjects

	Mean	Range	SD
$t_{1/2}\beta$ (h)	8.2	0.5– 38.9	7.9
Vd (l/m^2)	160	26 –585	105
$AUC_{0-\infty}$ (ng/ml/h per mg/kg)	78	16 –182	55

half-life, $t_{1/2}\beta$ (Table 2). Hence, since $\infty \gg \beta$ the disposition and elimination of vincristine rapidly approaches that described by a single-compartment model:

$$c_p = B_{\exp}{}^{-\beta t}. \quad [3]$$

Accordingly, $t_{1/2}\beta$, Vd, and $AUC_{0-\infty}$ were determined for each patient studied.

Pharmacokinetic analysis of drug concentration versus time curves resulting from the first analysis for each patient revealed wide interindividual differences in $t_{1/2}\beta$, Vd, and $AUC_{0-\infty}$ (Table 2). Fifteen patients were found to have abnormally high serum alkaline phosphatase concentrations on at least one occasion of vincristine plasma concentration analysis. Table 3 shows a comparison of vincristine pharmacokinetic parameters determined for these patients with those obtained from the 31 patients whose serum alkaline phosphatase levels were within normal limits. It can be seen that raised serum alkaline phosphatase is

Table 3. The effect of raised serum alkaline phosphatase on the pharmacokinetics of vincristine[a]

	Raised alkaline phosphatase ($n = 15$)[b]		Normal alkaline phosphatase ($n = 31$)[b]
$AUC_{0-\infty}$ (ng/ml/h)	145 ± 88	$P < 0.001$	54 ± 35
$t_{1/2}\beta$ (h)	13.0 ± 10.8	$P < 0.001$	5.1 ± 3.5
Vd (l/m^2)	163 ± 131	n.s.	165 ± 105
Dose (mg/m^2)	1.2 ± 0.3	n.s.	1.1 ± 0.3

[a] Significance of difference determined according to the unpaired *t*-test
[b] Mean values shown with standard deviations

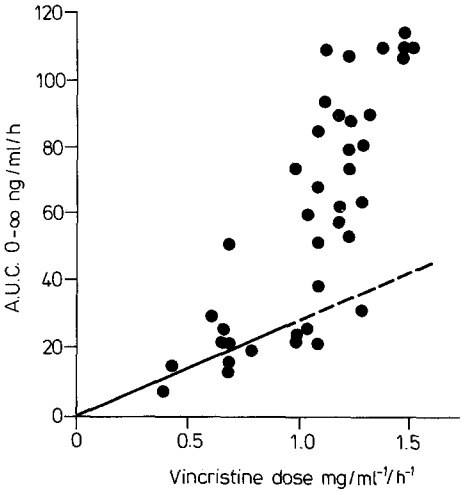

Fig. 2. The relationship between vincristine $AUC_{0-\infty}$ and dose for those patients with serum alkaline phosphatase concentrations within normal limits at the time of assay

associated with a highly significant increase in both vincristine $AUC_{0-\infty}$ and $t_{1/2}\beta$. There was no significant difference in either mean Vd or mean dose between the two groups (Table 3). Three patients with raised serum alkaline phosphatase had hyperbilirubinaemia. Serum γ-glutamyl transferase activity was determined in eight of the fifteen patients with raised serum alkaline phosphatase and raised levels of both enzymes occurred on seven occasions.

Figure 2 demonstrates the relationship between vincristine dose and $AUC_{0-\infty}$ on those occasions when serum alkaline phosphatase was within normal limits at the time of vincristine determination. There was a good correlation between dose and $AUC_{0-\infty}$ up

Table 4. The effect of dose on the pharmacokinetics of vincristine in patients with serum alkaline phosphatase concentrations within normal limits[a]

	Dose 1 mg/m^2 or less ($n = 13$)[b]		Dose > 1 mg/m^2 ($n = 26$)[b]
$t_{1/2}\beta$ (h)	2.9 ± 1.3	$0.1 > P > 0.05$	6.9 ± 7.4
Vd (l/m^2)	133 ± 78	n.s.	181 ± 127

[a] Significance of difference determined according to the unpaired *t*-test
[b] Mean values shown with standard deviations

to a dose of 1 mg/m^2 ($r = 0.82$). In the majority of patients who received a dose > 1 mg/m^2 the $AUC_{0-\infty}$ was considerably higher than that predicted by extrapolation of the regression line determined for doses up to 1 mg/m^2. A comparison of $t_{1/2}\beta$ and Vd resulting from treatment with vincristine up to a dose of 1 mg/m^2 with those parameters determined following administration of > 1 mg/m^2 vincristine is shown in Table 4. Whilst there was no significant difference in mean Vd between the two groups, administration of vincristine at doses > 1 mg/m^2 resulted in a mean $t_{1/2}\beta$ more than twice as long as that observed for the group receiving 1 mg/m^2 vincristine or less.

Discussion

The pharmacokinetics of vincristine in 39 patients has been investigated following administration of the drug in the dose range 0.4–1.54 mg/m^2 as part of conventional treatment protocols. The data obtained from serial measurements of vincristine plasma concentration following IV bolus administration could be fitted to a two-compartment pharmacokinetic model, and wide interindividual variation in the length of $t_{1/2}\beta$ and the associated Vd were observed. This variability resulted in an 11-fold variation in the dose-corrected area under the drug concentration-time curve delineated by the terminal elimination phase (Table 2). In contrast to the results of earlier studies in a smaller group of patients [6], our data did not warrant employing a more complex three-compartment pharmacokinetic model. There is, however, a measure of agreement between the pharmacokinetic parameters for vincristine reported in the studies of Nelson et al. [6] and the data presented in this paper. Thus, the mean volume of distribution associated with the terminal elimination

phase indicates extensive tissue binding of vincristine, and distribution is rapid compared with elimination. The mean half-life of the terminal elimination phase derived from our studies (Table 2) is considerably shorter than that previously reported [6], although the study of Nelson et al. also demonstrated a high degree of interpatient variability ($t_{1/2}$ = 85.0 ± 68.9 h). Our study has identified two variables that may be partly responsible for the observed overall interpatient variability in dose-corrected vincristine $AUC_{0-\infty}$. Data have been presented that strongly suggest that the elimination of vincristine, and consequently $AUC_{0-\infty}$, is influenced by liver function status as indicated by serum alkaline phosphatase activity. Whilst bone may also be a source of alkaline phosphatase, none of the breast cancer patients in our study presented with raised levels of this enzyme and when serum γ-glutamyl transferase activity was also assessed there was good agreement between the levels of the two enzymes, suggesting that alkaline phosphatase was hepatic in origin. Raised serum alkaline phosphatase was associated with a significantly prolonged vincristine elimination half-life and higher $AUC_{0-\infty}$ than were determined in subjects with serum alkaline phosphatase within normal limits (Table 3). Since there was no significant difference in Vd between the two groups and raised serum alkaline phosphatase is often indicative of cholestatis, we conclude that the correlation between elevated serum alkaline phosphatase and reduced clearance of vincristine reflects impairment of biliary elimination of the drug.

Patients in this study received between 0.4 and 1.54 mg vincristine/m^2, and pharmacokinetic data indicated a disproportionate rise in vincristine $AUC_{0-\infty}$ at doses in excess of 1 mg/m^2 (Fig. 2). Dose-dependency of pharmacokinetic parameters (zero-order kinetics) may result from saturation of tissue-binding sites leading to a decrease in volume of distribution with increasing dose. This does not appear to explain the disproportionate rise in vincristine $AUC_{0-\infty}$ with increasing dose, since there was no significant difference in Vd between the 'low-dose' and 'high-dose' groups (Table 4). Saturation of the processes involved in drug elimination may also lead to a deviation from normal first-order kinetics within the therapeutic dose range. We have found that patients receiving a dose of vincristine greater than 1 mg/m^2 had a mean $t_{1/2}\beta$ more than twice as long as the mean value for the group of patients receiving 1 mg/m^2 or less (Table 4). A recent study of the effect of vinca alkaloids on the secretion of biliary lipids and bile flow may provide an explanation for the observed decreased clearance of vincristine at high dose levels. Gregory et al. [4] observed that vinblastine significantly inhibited the biliary excretion of lipids and bile flow and postulated that this effect was a result of alkaloid-induced damage to the hepatocyte microtubular network, which is thought to be involved in biliary transport. Since the vinca alkaloids are themselves excreted in the bile [5, 8], it is possible that in the higher dose range vincristine damages the transport system involved in its own elimination in such a way that excretion becomes self-limiting. Further investigation in this area is necessary, since we cannot exclude the possibility that those patients who received the higher doses of vincristine in our study were intrinsically less efficient at eliminating the drug than those patients to whom the lower doses were administered.

Since the majority of patients in this study received vincristine in combination with other cytotoxic drugs or hormones, the possibility of drug interactions must be considered. Treatment protocols were not changed to facilitate the study, so that it was not possible to assess the influence of any particular co-administered drug. Nevertheless, the effect of serum alkaline phosphatase levels and dose on vincristine pharmacokinetics described could not be explained by differences in treatment protocols between the groups of patients being compared.

We have identified two factors that may independently give rise to elevated plasma levels of vincristine – biochemical evidence of liver disease and deviation from first-order pharmacokinetics within the therapeutic dose range. Increased incidence of toxicity in patients with evidence of liver dysfunction has been observed previously [9], and the data presented in this paper provide a pharmacokinetic basis for this clinical observation. Similarly, the observed marked increase in neuropathy with modest increases in dose could be explained by our data, which suggest that clearance may be impaired with increasing dose. These suggestions have received further support from our studies of the relationship between vincristine pharmacokinetics and the incidence and severity of peripheral neuropathy, which are presented in the companion paper [2].

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